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A prospective case-control study of cystatin-C levels in hypertensive pregnant patients in Benin City, Nigeria

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Abstract

Hypertension, often referred to as high blood pressure, poses a significant health threat, especially in pregnant women. This prospective case-control study conducted in Benin City, Nigeria, investigates the levels of Cystatin-C in hypertensive pregnant patients. Hypertensive disorders during pregnancy, affecting 2 to 10 pregnancies out of 10, can lead to severe health complications for both the mother and the unborn child. Pregnancy-induced hypertension, in particular, is a leading cause of maternal mortality worldwide and is associated with various chronic health conditions. Monitoring blood pressure is crucial in identifying individuals at risk and managing the consequences of hypertension, as it is a significant risk factor for cardiovascular and kidney diseases. The study focused on the potentials of Cystatin-C, a marker for kidney function, to provide insights into renal health in hypertensive pregnant patients. The research involved 190 women categorized into three groups: preeclampsia, pregnancy-induced hypertension, and normotensive pregnant individuals. In order to estimate the amounts of urea, creatinine, and Cystatin-C, blood samples were drawn and blood pressure was measured. The findings revealed that Cystatin-C levels were significantly elevated in preeclamptic cases compared to normotensive individuals. The results also indicated that Cystatin-C levels in preeclampsia increased during the third trimester. Additionally, there was a significant influence in body mass index of Cystatin-C levels, and higher levels observed in individuals with lower body mass index, BMI.

Keywords: Pregnancy-induced hypertension, cystatin-C, preeclampsia, renal function, blood pressure, maternal health, hypertensive disorders, biomarker

1. Introduction

One prevalent medical condition that affects a significant percentage of pregnant women worldwide is hypertension. Approximately 2 to 10 pregnancies out of every 10 have hypertension, which is a frequent medical problem during pregnancy. Hypertension, often know as elevated blood pressure, served as a disorder that causes higher levels of blood pressure that has serious health effects. Nearly 30,000 pregnant women worldwide are affected by this illness, according to the statistics accessible (1,2). Being pregnant and having hypertension is dangerous since it can have negative effects on the mother and the unborn baby. The degree of these consequences might range from small inconveniences to dangerous circumstances. Pregnancy is a major contributor to maternal and fetal mortality due to hypertension. In the world, it ranks behind diseases like AIDS, diabetes, and postpartum hemorrhage as the third most prevalent cause of maternal mortality. Additionally, chronic health issues including renal failure, persistent hypertension, and cardiovascular system diseases have all been connected to hypertension during pregnancy (3,4).

A systolic or diastolic blood level of 90mm Hg and 140 mm Hg or above is considered to be hypertension in pregnancy. Elevated level of blood pressure occurs in pregnant woman lead to an emergency medical condition that has to be treated right away. Regarding both the mother as well as the child, this disorder has the potential to cause serious difficulties. Pregnancy-related hypertension increases the chance of the condition occurring later on in life, frequently serving as a warning sign for prospective heart and vascular problems. Serious consequences for the mother from high blood pressure during pregnancy might include cardiac arrest, stroke, and injury to crucial organs including the renal system, respiration, or liver. Additionally, it can result in potentially fatal diseases including preeclampsia, convulsions, and premature birth (5).

Pregnancy-related hypertension can have a variety of effects on the developing infant. It could result in preterm birth, low birth weight, and labor problems that might call for an impromptu epidural. In extreme circumstances, it may contribute to a stillbirth, in which the infant dies during delivering. Pregnant women should be profiled to determine

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who is at risk of having hypertensive problems throughout the course of pregnancy because high blood pressure while pregnant is still a serious worry. To ensure that effects of high blood pressure on both mother and infant effects, this is essential. A report from the World Health Organization (6), up to fifteen percent of pregnancy and postpartum problems are significantly influenced by hypertension. Preexisting (or chronic) high blood pressure, gestational hypertension, preeclampsia, and eclampsia are the illnesses included by this group, which jointly affects between 5 and 10 percent of women of age at conception (7, 8).

Blood pressure (BP) fluctuations may have extra therapeutic importance, as hypertension lead to significant development complication related to cardiovascular as well as kidneys illnesses. Given the nocturnal reduction in hypertension, there are four categories of circadian blood pressure patterns: reverse dipper, severe dipper (more than 20% Systolic fall), non-dipper (10% Systolic fall), and dipper (10% to 20% SBP decrease). The functioning of the kidneys is crucial for both a normal pregnancy and preeclampsia. Preeclampsia term pregnancies frequently prompt alterations in renal function. Clinicians must overcome the problem of making a prompt identification of renal impairment in order to stop progression in fetal morbidity and death into eclampsia (9). The level of hypertension should still be categorized as hypertension even when it is lower than 140/90 mmHg since the patient has history related to the condition which receiving antihypertensive medication (10-12). Nevertheless, kidney damage remains one of most significant side effects of hypertension and is intimately connected to the reduction of the natural drop in nocturnal blood Pressure. According to reports, hypertension patients' nighttime blood pressure has a more important prognostic function in predicting their probability of experiencing clinical episodes (13-16).Creatinine levels in the blood are frequently employed during medical settings as a marker to evaluate kidney function. The kidneys remove it from the blood as a consequence of the breakdown of muscle tissue. Rule et al found that a reduction in glomerular filtration rate (GFR) is frequently correlated via an increase in blood creatinine levels. Particularly in instances of acute renal damage or when blood creatinine might not be reliable, serum cystatin C is regarded as an important measure for evaluating kidney function. It provides an additional thorough assessment of renal health than various laboratory tests and medical information (17-19).

Nearly all living cells spontaneously make cystatin C, a compound that inhibits protease having molecular weight of 13 kilodaltons that is efficiently screened through the kidney's glomerulus. The level of creatinine are more affected through characteristics including age, sex, and physique than cystatin C, as a result, it is thought to be a more accurate measure for determining glomerular filtration rate, particularly in people who have experienced recent renal damage (20, 21).This quality is especially important for patients with hypertension since they are more likely to experience deteriorating renal function due to ineffective blood pressure. For individuals with vital hypertension, the finding that serum cystatinC (s-CC) acts as an individual threat for target-organ deterioration as well as cardiovascular diseases is important. It draws attention to the cystatin C potential therapeutic applications outside being utilized as a kidney function marke (18, 19, 22, 23).

While addressing those with crucial hypertension, physicians must take a variety of parameters into account, and cystatin C screening might be useful tool to the diagnostic and treatment toolset. This study focuses on the potential of Cystatin-Cs, which served as marker for kidney operation, to provide insights into renal health in hypertensive pregnant patients. The research involved 190 women categorized into three groups: preeclampsia, pregnancy-induced hypertension, and normotensive, normal pregnant individuals. Blood was drawn for the assessment of urea, creatinine, and Cystatin-C levels, and blood pressure was measured.

Preeclampsia and hypertension caused by pregnancy are two examples of hypertensive diseases in childbirth that pose a serious worldwide health risk. Serious consequences, such as as premature birth, low birth weight, and damage to the mother's organs, can result from these diseases affecting the mother and the fetus. Enhancing maternal and fetal health results requires understanding underlying processes and identifying early indicators for these illnesses. The study explores the use of Cystatin-Cs as biomarker for assessing kidney functioning in hypertensive pregnant patients. While creatinine has traditionally been used for this purpose, Cystatin-Csshown promise ofmore accurate indicator of kidney functioning in specific situations, including cases of acute renal damage. Understanding the role of Cystatin-C in pregnancy-induced hypertension can provide valuable information for clinical practice and potentially lead to more accurate and early diagnosis of kidney dysfunction in these patients.

If Cystatin-Cs found as reliable marker for kidney dysfunction in hypertensive pregnant patients, it can aid in early detection and better management conditions. However, this could lead to a reduction in complications and improved outcomes for mothers and their babies

2. Material and Methods

This prospective case-control study was conducted at the Department of Obstetrics and Gynecology, Central Hospital, and University of Benin Teaching Hospital, both in Benin City, Nigeria. A total of 190 women participated in the study, which comprised three groups: a preeclampsia group (n = 124), a pregnancy-associated hypertension group (n = 30), and a normotensive, healthy pregnant group (n = 36). Women with a history of cardiovascular disease, kidney disease, thyroid disease, diabetes mellitus, hepatic disease, or other related disorders, including urinary tract infections (UTIs), were excluded from the analysis.

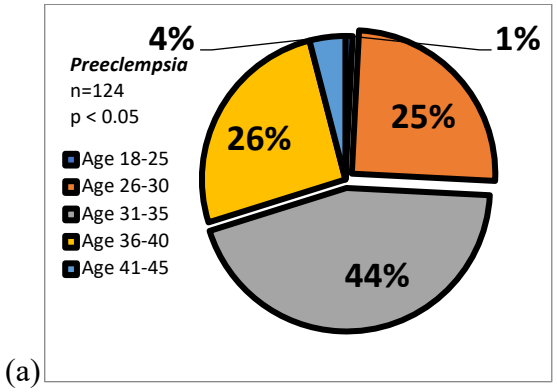
Blood pressure measurements were taken using a mercury sphygmomanometer, with each participant lying flat, on at least two occasions. Venous blood samples (5 ml) were collected from each participant via a single antecubital venipuncture using a sterile disposable syringe. The blood was then processed to isolate plasma, which was transferred to a 5 ml plain vial using a Pasteur pipette after being drawn into a heparinized bottle. The plasma samples were stored at -4°C prior to analysis. Cystatin C plasma concentrations were determined using the enzyme-linked immunosorbent assay (ELISA) method. Creatinine and urea concentrations were measured using the modified Jaffes Principle and the urease method, respectively (24, 25).

2.1. Method of Data Management and Statistical Analysis

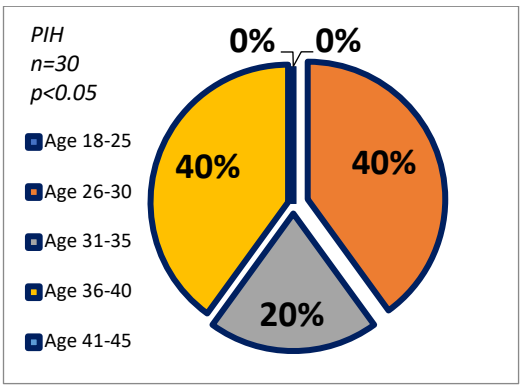
Statistical analysis of the data was performed using SPSS, version 23 (IBM Corporation, USA). The results are presented as mean ± standard deviation (SD). To determine significant differences among the preeclamptic, pregnancy-induced hypertension (PIH), and normotensive groups, a one-way ANOVA (Analysis of Variance) was used. Additionally, an independent t-test was employed to compare the analyte composition of preeclamptic patients based on disease severity (severe vs. mild). Other results are presented in chart format.

3. Results

Results in Fig.1 showed age groups of pregnancy-induced hypertensive patients, pre-eclamptic patients and control groups respectively. Results showed that 44% of the respondents accounted from pre-eclamptic patients that were within the 31-35 years age category, while for the same group 20% were pregnancy-induced hypertensive patients. Of the 124 preeclamptic subjects, 71 were overweight and 30 obese (Fig. 2). Majority of the preeclampstic patients had weight issues. However, only few of the respondents who had pregnancy-induced hypertension were either obese (n=4) or overweight (n=3), compared to the normotensive group (n=23). Fig. 3 presents the risk incidence factors for preeclamptic participants in the study. Here, the most significant risk factor was family history of preeclamsia (91.2%); this was followed by remarriage (89.3%) and edema (81.1%). For those with previous history of preeclampsia, prevalence was 43.7%. the demographic information of the study participants have been presented on Table 1.



(a)



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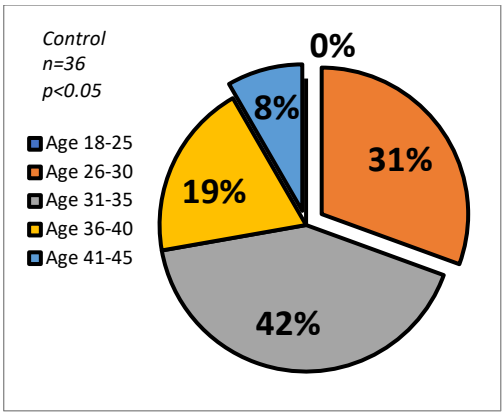

(c)

Fig. 1. Age groups (a) pre-eclamptic patients (b) pregnancy-induced hypertensive patients and (c)control

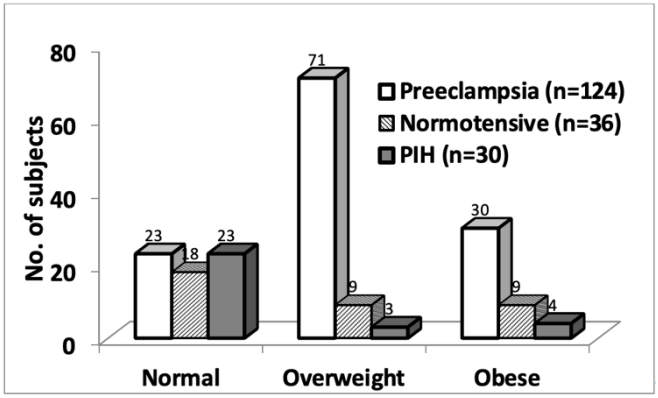

Fig. 2. Show percentage distribution of respondents on the basis of body mass index

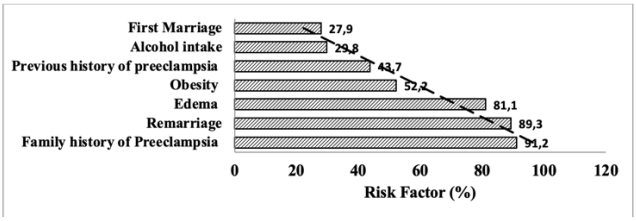

Fig. 3. Risk incidence factors for preeclamptic participants in the study

Table 1. Demographic data of respondents

Queries	Preeclampsia cases (A) n (%) (N=124)	Normotensive (B) n (%) (N=36)	PIH(C) n (%) (N=30)	(A+B)	(A+C)	(B+C)
				p-values		
Marital status						
Single	3 (2.4)	2 (5.6)	0	0.323	0.032*	0.041*
First Marriage	92 (74.2)	33 (91.7)	10 (100)	0.041	0.006*	0.032*
Remarried	29 (23.4)	1 (2.8)	0	0.013	0.027	0.072
Religion						
Christianity	122 (98.4)	20 (55.6)	10 (100)	0.006*	0.713	0.031*
Islam	2 (1.6)	16 (44.4)	0	0.001*	0.742	<0.001*
Others	0	0	0	0	0	0
Educational status						
None	4 (3.2)	0	0	0	0	0
Primary	17 (13.7)	3 (8.3)	3 (30)	0.442	0.441	0.989
Secondary	47 (37.9)	16 (44.5)	3 (30)	0.110	0.028*	0.001*
Post-secondary	56 (45.2)	17 (47.2)	4 (40)	0.142	0.146	0.083
Job status						
Employed	102 (82.3)	27 (97.5)	8 (80)	0.192	0.892	0.173
Unemployed	22 (17.7)	9 (2.5)	2 (20)	0.014	0.070	0.009*
Job type						
Business owner/Trader	86 (69.4)	26 (72.2)	9 (90)	0.211	0.045*	0.064
Civil servant	16 (12.9)	5 (13.9)	0	0.791	0.001*	0.001*
House wife	22 (17.7)	5 (13.9)	1 (10)	0.075	0.051	0.103

*significant

Table 2. Grouped data (totals) for analytes of respondents presented irrespective of trimester used for assessing kidney function

Queries	Preeclampsia cases (A) (µ±SEM) (n=124)	Normotensive (B) (µ±SEM) (n=36)	PIH(C) (µ±SEM) (n=30)	p-value (A+B)	p-value (A+C)	p-value (B+C)
Cystatin-C (ng/mL)	1.99±0.10	1.42±0.19	1.83±0.27	0.012	0.685	0.025
Plasma Urea (mg/dL)	33.96±2.23	23.54±0.72	35.80±3.21	<0.001	0.173	0.004
Plasma-Creatinin (mg/dL)	0.90±0.19	0.79±0.31	0.76±0.64	0.013	<0.001	0.182

Table 2 presents the grouped data (totals) for analytes of respondents presented irrespective of trimester used for assessing kidney function. Cystatin-C concentration in preeclamptic cases was 1.99ng/mL. This value was significantly higher ($p<0.05$) than the normotensive value 1.42 ng/mL. However, cystatin- C value in preeclamptic cases did not significantly differ from pregnancy-induced hypertensive cases. Plasma urea value in the preeclamptic (PRE) cases (33.96 mg/dL) significantly differed from normotensive (23.54 mg/dL); similarly pregnancy-induced hypertensive (PIH) cases (35.80 mg/dL) were comparatively than the control. Incidentally, urea value in PIH was higher than in PRE. Inspite of these changes, urea values for these three groups fall within expected range used in medical practice in the medical facility where samples were collected (maximum 40 mg/dL). Plasma Creatinine value in PRE was 0.90 mg/dL; this was higher than in the normotensive cases (0.79 mg/dL). Creatinine between and normotensive and PIH cases did not differ significantly ($p>0.05$).

Table 3. Analytes of respondents presented on the basis of trimesters for assessment of kidney function. Only means of replicates have been presented

Queries	Trimester	Preeclampsia cases (A) (µ±SEM) (n=124)	Normotensive (B) (µ±SEM) (n=36)	PIH(C) (µ±SEM) (n=30)	(A+B)	(A+C)	(B+C)
					p-values		
Cyst-C (ng/mL)	Second	1.144	1.491	2.408	0.086	<0.001	0.002
	Third	2.851	1.368	1.271	<0.001	0.001	0.092
Plasma Urea (mg/dL)	Second	24.479	25.859	36.020	0.472	<0.001	0.031
	Third	22.613	40.445	35.590	<0.001	0.005	0.042
Plasma-Creatinin (mg/dL)	Second	0.904	0.737	0.800	0.004	0.279	0.059
	Third	0.911	0.710	0.740	0.031	0.109	0.137

Analytes of respondents presented on the basis of trimesters for assessment of kidney function have been presented (Table 3). During the second trimester, cystatin C concentration at PRE did not significantly differ from those in the control group. However, during the third trimester, significant elevation in cystatin C value was observed. This value at PRE was also higher than at PIH during the third trimester (Table 3). Plasma creatinine contents at second (0.904 mg/dL) andthird (0.911 mg/dL) trimesters were significantly elevated in PRE cases compared to control group (0.737 mg/dL).

Table 4. The analyte composition of preeclamptic patients was divided based on the disease's severity

Analytes	Groups	N	Mean	Std. Error Mean	p-value
Cyst-C (ng/mL)	Mild	38	2.2094	0.2023	0.212
	Severe	84	1.9177	0.1276	
Plasma Urea (mg/dL)	Mild	38	23.28	1.5644	0.809
	Severe	84	23.661	0.7886	
Plasma-Creatinin (mg/dL)	Mild	38	0.8519	0.0384	0.067
	Severe	84	0.9283	0.0218	

Analyte composition results of preeclamptic individuals divided according to illness severity (Table 4). Cystatin C urea and creatinine levels did not significantly differ between individuals with mild and severe PRE. The levels of creatinine and cystatin C urea were unaffected by the severity of PRE. While urea and creatinin were within acceptable ranges, cystatin-C was generally and observably high in PRE continuously. It was discovered that body mass index (BMI) had an impact on Cystatin C ($p<0.05$). As BMI grew, cystatin C readings were consistently lower (Table 5). The values of cystatin C were 1.77 ng/mL in individuals who were obese, 2.59 ng/mL in the control group, and 1.899 ng/mL in the overweight patients.

Table 5. Comparing analyte composition of preeclamptic subjects separated on the basis of BMI

	Group 1 – Normal vs Overweight					Group 2 – Normal vs Obese				
		N	Mean	SEM	p-value		N	Mean	SEM	p-value
Cyst_C(ng/mL)	Normal	23	2.5969	0.235	0.016	Normal	23	2.5969	0.235	0.013
	Overweight	71	1.8991	0.142		Obese	30	1.7743	0.215	
Urea(mg/dL)	Normal	23	20.2235	2.237	0.061	Normal	23	20.224	2.237	0.051
	Overweight	71	23.9744	0.865		Obese	30	25.082	1.258	
Creatinine (mg/dL)	Normal	23	0.8967	0.058	0.609	Normal	23	0.8967	0.058	0.81
	Overweight	71	0.9236	0.023		Obese	30	0.88	0.041	

4. Discussion

Hypertension, or high blood pressure, is a health condition that carries significant risks for pregnant women. This study, set in Benin City, Nigeria, addresses the critical issue of hypertension during pregnancy, which poses serious health threats to both mothers and their unborn children. Pregnancy-related hypertension issues are very common, affecting 2 to 10 pregnancies out of every 10. It's estimated that nearly 30,000 pregnant women worldwide are affected by this condition, making it a pressing global concern (1).

Induced hypertension during pregnancy in particular, showed to be a leading cause in maternal mortality worldwide and is associated with various chronic health conditions (4). Hypertensive disorders during pregnancy, such as preeclampsia, can lead to complications ranging from mild inconveniences to severe and potentially fatal outcomes. These include cardiac arrest, stroke, damage to vital organs like the kidneys, liver, and respiratory system, as well as fatal conditions like preeclampsia, convulsions, and premature birth (8).

One of the primary organs affected by hypertension is the kidneys. Hypertension can lead to kidney damage, and monitoring kidney function is crucial in the context of hypertensive pregnant patients. Cystatin-C is introduced in the research as a kidney function marker, highlighting its potential offer insights into renal health in this patient population. Traditionally, creatinine levels in the blood have been used to assess kidney function, as the kidneys remove creatinine from the blood as a result of muscle tissue breakdown. However, cystatin C is proposed as a more accurate measure for determining glomerular filtration rate (GFR), particularly in cases of acute renal damage or when blood creatinine levels may not be reliable (18, 19). In individuals with hypertension, cystatin-C can lead to risk factor for target-organ damage as well as cardiovascular illness, adding an additional layer of diagnostic and prognostic value (22, 23).

The study involved 190 pregnant women categorized into three groups: preeclampsia, pregnancy-induced hypertension, and normotensive, normal pregnant individuals. Blood pressure measurements were taken, and sample of blood were obtained to estimate Cystatin-C, creatinine, and urea levels. The findings revealed that Cystatin-C levels was significantly elevated in pre-eclamptic cases contrasted to normotensive individuals. This suggests that Cystatin-C could be a valuable marker for identifying kidney dysfunction in hypertensive pregnant patients. Furthermore, according to the study cystatin-C values in preeclampsia increased notably during the third trimester, emphasizing the importance of monitoring

renal health throughout pregnancy. The examination of the relationship between body mass index (BMI) and Cystatin-C levels is a fascinating feature of this study. The results indicate a significant impact of BMI, with higher Cystatin-C levels observed in individuals with lower BMI. This finding opens up potential avenues for further research in the relationship between body composition and renal health in pregnant women with hypertension.

The study also examined whether the severity of preeclampsia influenced Cystatin-C, urea, and creatinine levels. Surprisingly, there were no significant distinctions in these analytes between patients with mild and severe preeclampsia, suggesting that Cystatin-C may be consistently elevated, regardless of the severity of the condition. Incidentally, the study found that Cystatin-C concentrations in preeclamptic cases did not significantly differ from the control group observed during the second trimester. Nonetheless, a notable increase in Cystatin-C levels was noted in preeclamptic individuals throughout the third trimester, underscoring the need of keeping an eye on renal function as pregnancy advances. The study also explored the demographic and threat factors related to preeclampsia. The study shows that a family history of preeclampsia, remarriage, and edema were the most significant risk factors among the participants. This demonstrates the intricate interaction between environmental and genetic variables that leads to the development of hypertension problems in pregnancy.

In summary, our work sheds important light on the function of cystatin-C as a putative kidney function measure in hypertensive pregnant individuals, particularly those who have preeclampsia. The results indicate that preeclamptic patients had considerably higher levels of Cystatin-C, with considerable alterations occurring during the third trimester. The study also emphasizes how BMI affects Cystatin-C levels, with lower BMI being linked to greater levels of Cystatin-C. These results have implications for the early detection and treatment of renal failure in pregnant women with hypertension, which is essential to avoiding serious consequences. More resources for vulnerability assessment and intervention may be made available by more study in this field.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: M.U., T.A., Design: AK, O- S.O.E., Data Collection or Processing: A.K., Analysis or Interpretation: O-S.O.E., Literature Search: A.K., O-S.O.E., O.E.S., Writing: A.K., O-S.O.E., O.E.S.

Ethical Statement

Every participant in the research gave their informed permission. The nature and aim of this work were fully discussed with study participants and had the right to withdraw from the study without being adversely affected regarding the medical service they received. Ethical approval of ethical committee (Protocol No. ADM/E.22/A/VOL.VII/1469) was also collected from the University of Benin Teaching Hospital, Edo State.

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